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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,124	12/27/2005	Stanley R Terlecky	TERLECKY1A	5930

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EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,124	TERLECKY ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,17-21,23,24,26,29,34-36,41,42,45-47,49-53,56 and 59-61* is/are pending in the application.

4a) Of the above claim(s) *17-19,23,24,26,29,34,36,42,45-47,49-53 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,9-12,20,21,35,41 and 58-61* is/are rejected.

7)☒ Claim(s) *3-8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 13-16, 22, 25, 27, 28, 30-33, 37-40, 43, 44, 48, 54, 55, 57 and 58 have been canceled. Claims 1-12, 17-21, 23, 24, 26, 29, 34-36, 41, 42, 45-47, 49-53, 56, 59 and new claims 60-61 are at issue and are present for examination.

Claims 17-19, 23, 24, 26, 29, 34, 36, 42, 45-47, 49-53, and 56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/18/08.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 9-12, 35, 41, 58, and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sheik et al. in view of Trelease et al. The rejection is explained in the previous Office Action.

Applicants argue that a sufficient *prima facie* case of obviousness has not been made because the cited art does not suggest that the present compositions and methods and lacks a motivation to combine Sheikh with Trelease, and further, with Fujiwara. This not persuasive as both Sheik et al. and Trelease et al. teach methods of introducing catalse activity into peroxisomes using a catalase variant with a modified peroxisomal targeting sequence. Thus these references are clearly analogous art and properly combinable. Sheik et al. clearly show that the introduction of the catalase variant normalized multiple peroxisomal functions of resulting from lack of catalse activity in mutant Zellwegger cells and thus a skilled artisan would be motivated to look for other similar modified catalse variants which would have similar properties. Given this a skilled artisan would look to disclosures such as that of Trelease et al. which teach other similar catalase variants with a modified peroxisomal targeting sequence. Thus motivation to combine Sheik et al. and Trelease et al. is clearly present.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue that Sheik et al. teach adding the SKL peptide to the naturally occurring KANL sequence and thus do not suggest replacing the KANL sequence with the SKL peptide. However, while this argument might be applicable if Sheik et al. were considered alone, the disclosure of Trelease et al. clearly shows that replacement is also an option. Applicants further referred to other portions of Sheik et al. which they contend teach away from the claims, specifically, Sheikh's teaching that Cat has a peroxisomal import pathway that is independent of either the PTS1 receptor or the PTS2 receptor. However, the suggestion of an additional peroxisome import pathway of catalase in no way teaches away from modifying catalase to include a PTS1 targeting signal to improve its import by the PTS1 pathway such that one can normalize peroxisomal functions in mutant cells in which the natural (possibly different) peroxisomal import pathway clearly does not function sufficiently. Merely because Sheik et al. provided one

particular modified catalse variant sequence which accomplished this would not have prevented a skilled artisan from making other such variants which could be reasonably expected to be similarly successful at normalizing the peroxisomal functions of mutant cells. Nothing in Sheik et al. in fact teaches away from making a replacement variant such as that of Trelease et al. A teaching away would be a disclosure which suggested that a replacement variant would not function or should not be made, not merely a teaching of making a different variant. If every teaching of something different than what was claimed was in fact a teaching away, nothing would ever be obvious as in any 103 rejection necessarily there is something that is different in each reference from what is claimed. If there weren't a difference the reference would be art under 102. In the Board case cited by applicant such a teaching away was in fact present as the rejection required optimization of the viscosity by increasing the viscosity while the prior art taught the low viscosity was desirable. Thus the art in fact pointed to doing exactly the opposite of what would be necessary. Here no such teaching in a contrary direction is present.

Applicants also argue that Trelease et al. teach away from the instant invention by stating that "the C-terminal tripeptide ANL-COOH was necessary and sufficient for peroxisome

targeting.". However, this is not persuasive as this statement is discussing the peroxisome targeting of unmodified catalse not the targeting of the modified catalse variant taught by Trelease et al. This is clearly evident as the modified variant of Trelease et al. does not even have a C-terminal ANL tripeptide. Trelease et al. clearly indicate that it is the C-terminal SHL tripeptide that is necessary and sufficient for the peroxisome targeting of the RcatSHL variant.

Applicants state that at the interview, Applicant pointed out that at most Trelease suggests that either the native KANL or SHL would result in some degree of peroxisomal targeting. However, because there is no suggestion that one targeting signal is better than the other in targeting rat catalase, one of ordinary skill in the art would have had no reason to alter the native C-terminal sequence in rat or human catalase. In response, the Examiner then asserted for the first time that the ordinary artisan would know that, in the context of different nucleic acid or protein functions, modifying a sequence to be more like the "canonical consensus sequence" would improve the function of the nucleic acid or protein. Applicants argue that this new assertion is the only basis for the suggestion that it would have been "obvious to try" the modified human catalase of claim 1 and to the extent the Office's position regarding

obviousness now relies on this assertion, it clearly constitutes a new ground of rejection. However, while this position may have been first raised during the interview, it is clearly NOT necessary for the instant rejection as the combination of Sheik et al. and Trelease et al. would have been motivated as discussed above. This merely provides an additional motivation for the combination. Furthermore, as this assertion is not necessary for the rejection and applicants have had ample opportunity to respond to this assertion, it clearly is not grounds to make the instant action non-final. Applicants further argue that the examiners statement at the interview that the ordinary artisan would know that modifying a variety of consensus sequences to be more like the canonical consensus improves the function of the sequence, examples of which are The rejection is explained in the previous Office Action. found for promoters, Shine-Dalgarno sequences, signal sequences, etc. is unsupported in the record. However, evidence of the truth of the examiner's statement is easily found in the prior art. For example, see US Patent 5,824,469, column 6, lines 6-25 and column 15, lines 52-67 (promoters), US Patent 6,057,136, column 39, lines 44-60 (Shine-Dalgarno sequences), and US Patent 6,159,170, column 30, lines 47-50 (splicing sequences) and the rejection of new claims 60-61 presented below.

Claims 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sheik et al. in view of Trelease et al. as applied to claims 1-2, 9-12, 35, 41, 58, and 59 above, and further in view of Fujiwara et al. The rejection is explained in the previous Office Action.

Applicants argue that Fujiwara does not compensate for the deficiencies of Sheikh and Trelease noted above nor does it add the requisite disclosure to apply it to pharmaceutical composition claims. However, as discussed above there are no deficiencies in the disclosures of Sheik et al. and Trelease et al. for making a *prima facie* case of obviousness of claims 1-2, 9-12, 35, 41, 58, and 59. Furthermore, the teachings of Fujiwara et al. that lack of proper transport of catalase to the peroxisomes of cells of patients with some peroxisome biogenesis disorders is linked to the inability of the mutant transport machinery of these patients to efficiently transport the non-standard PTS1 sequence of mammalian catalases even though the mutant transport machinery of these patients is capable of transporting sufficient amounts of other peroxisomal proteins having a typical PTS1 sequence clearly does provide motivation for a skilled artisan to prepare a modified catalse protein with a standard PTS1 transport signal to be administered to these patients. A skilled artisan would reasonably expect this

modified catalase variant to be useful for treating these patients as it would be expected to be correctly transported to peroxisomes in these patients as Fujiwara et al. teach that other peroxisomal proteins having standard PTS1 transport signals are correctly transported to peroxisomes in the cells of these patients. One of skill in the art would have been particularly motivated to do this given the combination of this disclosure with that of Sheik et al. that introduction of a catalase variant having a standard PTS1 peroxisome targeting signal into mutant Zellwegger cells normalized multiple peroxisomal functions of these cells resulting from lack of catalse activity.

Applicants argue that Fujiwara et al. conclusion that the defect in the cells of these patients is found in the import machinery and not in the catalase sequence teaches away from the instant invention. However, this is not persuasive because regardless of what the actual defect in the cells of these patients is, the disclosure of Fujiwara et al. that the result of the defect is catalase deficiency within the peroxisomes, combined with the disclosure that other peroxisome proteins with standard PTS1 transport signals are sufficiently transported and the disclosure of Sheik et al. that that introduction of a catalase variant having a standard PTS1 peroxisome targeting

signal into mutant Zellwegger cells normalized multiple peroxisomal functions of these cells clearly leads to an expectation that the peroxisome disorder could be treated with a variant catalase protein even if this treatment would not in fact correct the specific defect of the cells. Successful treatments of many known genetic diseases do not correct the defect but merely try to alter the consequences thereof. For example treatments of cystic fibrosis invariably attempt to reduce the characteristic viscous obstruction of the patients airways and not to actually alter the defective transporter that causes the disease. Here the art teaches that the consequence of the defect in the peroxisome import machinery is catalase deficient peroxisomes and the art suggests that a modified catalase with a standard PTS1 peroxisome targeting sequences would restore normal peroxisome functions and thus be expected to usefully treat the disease.

Claims 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sheik et al. in view of Trelease et al. and Fujiwara et al. as applied to claims 1-2, 9-12, 20, 21, 35, 41, 58, and 59 above, and further in view of Horowitz et al. (US Patent 5,824,469), Bower et al. (US Patent 6,057,136), and Fraser et al. (US Patent 6,057,136).

Sheikh et al. teach a human catalase variant in which a SKL peptide was added to the carboxy terminal leucine residue of the human catalase sequence. Sheikh et al. further teach the introduction of the variant catalase protein into cells and show the reduction of oxidation of several peroxisomal proteins and teach that this is likely due to the reduction of hydrogen peroxide levels in the peroxisomes of cells in which the variant catalase was present in the peroxisomes. Sheik et al did not remove the naturally occurring human KANL peroxisome targeting peptide but instead added the consensus PTS1 sequence i.e., SKL to the carboxy-terminus of the natural human KANL peroxisome targeting peptide.

Trelease et al. teach a rat liver catalase variant in which the carboxy terminal KANL peptide was replaced with an KSHL tripeptide. Trelease et al. further teach the introduction of the variant catalase protein into the peroxisomes of cells where it will reduce the hydrogen peroxide levels in the peroxisomes of the cells in which the variant catalase was present and that a carboxy-terminal SKL peptide is also a known peroxisome targeting signal.

Fujiwara et al. teach that lack of proper transport of catalase to the peroxisomes of cells of patients with some peroxisome biogenesis disorders is linked to the inability of

the mutant transport machinery of these patients to efficiently transport the non-standard PTS1 sequence of mammalian catalases even though the mutant transport machinery of these patients is capable of transporting sufficient amounts of other peroxisomal proteins having a typical PTS1 sequence. Fujiwara clearly suggest that even for normal mammalian cells the KANL PTS of catalase is not as efficiently recognized by the peroxisome transport proteins as are typical PTS sequences.

In view of the disclosure of Trelease et al. an ordinary skilled artisan would have understood that an alternative means of modifying the human catalase protein to a protein with a consensus PTS1 sequence i.e., SKL, as taught by Sheik et al. would be the replacement of the non-consensus KANL peptide with the consensus PTS1 peptide i.e., KSHL or KSKL and would have found it obvious to make a modified human catalase in which the KANL is replaced as claimed in order to use this modified protein for the normalization of peroxisomal functions in mutant Zellwegger cells. Furthermore, it would have been obvious make a pharmaceutical composition of the modified human catalase in order to treat a patient with peroxisome biogenesis disorders linked to the inability of the peroxisome transport machinery to efficiently transport the non-standard PTS1 sequence with modified human catalase which include the full catalase

catalytic domain but include a typical PTS1 sequence. However, the combined disclosure of Sheik et al., Trelease et al., and Fujiwara et al. to not clearly provide an expectation that the modified human catalase in which the KANL peptide is replaced with a standard PTS1 peroxisome targeting sequence (such as KSKL or KSHL) would be imported into peroxisomes at a rate that exceeds the import of native human catalase under the same conditions.

Horowitz et al. teach that mutations that increase homology with the consensus sequence promoter elements of the E. coli -10 and -35 regions increase transcription while mutations that decrease homology with the consensus sequence promoter elements decrease transcription. See particularly column 6, lines 6-25 and column 15, lines 52-67

Bower et al. teach that translation of genes in the *Bacillus subtilis* biotin biosynthetic operon can be improved by altering the ribosome-binding sites to conform more closely to a canonical *B. subtilis* ribosome binding site with the sequence 5'AGAAAGGAGGTGA3'. See particularly column 39, lines 44-60.

Fraser et al. teach that mutant mammalian cells carrying a gene with a consensus intron branch point sequence had an increased efficiency of splicing compared to cells carrying a

gene with a non-consensus intron branch point sequence. See particularly column 30, lines 47-50.

The combined disclosures of Horowitz et al., Bower et al., and Fraser et al. evidence that it is well known in the art that modifying a variety of consensus sequences for molecular biological functions to be more like the canonical consensus generally improves the function of the sequence. As such an ordinary skilled artisan would reasonably expect the same to be true of other sequences for molecular biological functions including the PTS1 peroxisomal targeting sequences of Sheik et al., Trelease et al., and Fujiwara et al. Therefore, an ordinary skilled artisan would have found it obvious to make a modified human catalase in which the KANL peptide is replaced with a standard PTS1 peroxisome targeting sequence (such as KSKL or KSHL) with a reasonable expectation that it would be imported into peroxisomes at a rate that exceeds the import of native human catalase under the same conditions.

Claims 3-8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed, can be reached at (571) 272-0934. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval

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/Rebecca Prouty/
Primary Examiner
Art Unit 1652